Amendments to the Specification

Please replace paragraph 0020 on page 5 with the following amended paragraph:

-- ~~Figure 3~~ Figure 4 depicts the predicted membrane-binding cap of FAAH; the sequence below Panel A represents residues 404-433 of SEQ ID NO: 1, with the hydrophillic residues at positions 409, 412, 415, 416, 419 423, and 429 of SEQ ID NO: 1 being denoted by "x" for purposes of illustrating the positioning of the hydrophillic residues in this region. --

Please replace paragraph 0021 on page 6 with the following amended paragraph:

-- ~~Figure 4~~ Figure 3 sets forth proposed modular adaptations that convert a soluble enzyme to an integral membrane enzyme based on differences in the structures of FAAH and MAE2. --

Please replace paragraph 0046 on page 18 with the following amended paragraph:

-- Amino acids 410 to 438 of SEQ ID NO: 1, another sequence insertion in FAAH relative to MAE2, form a helix-turn-helix motif that interrupts the AS fold. The two helices, α18 and α19, cap the active site and present several hydrophobic residues that likely compose FAAH's membrane binding face (Figs. 1, ~~3A~~ 4A). The *N*-terminus of the intact enzyme, predicted by sequence analysis to form an additional membrane-binding helix (amino acids 7-29), would be properly positioned to reinforce the membrane interactions of the α18 and α19 membrane cap (Fig. 1B). --

Please replace paragraph 0047 on page 18 with the following amended paragraph:

-- A potential substrate entryway is adjacent to α18 and α19, and the arachidonyl chain of MAP contacts phenylalanine 432 of α18, which may indicate direct access between the FAAH active site and the hydrophobic membrane bilayer. The putative substrate entry is amphipathic in nature with hydrophobic residues covering three sides of the rim and charged residues arginine 486 and aspartate 403 completing the remaining side (Fig. 2A, ~~3B~~ 4A). This arrangement of residues may accommodate the admission and movement of polar fatty acid amide head groups towards the active site. Overall,

the intimate relationship between the membrane binding surface and active site of FAAH is similar to that of squalene cyclase (*19*) and prostaglandin H_2 synthase (*20*) which also act upon lipid soluble substrates and have hydrophobic caps surrounding their respective active site entrances. In all three enzymes, the hydrophobic cap is surrounded by basic amino acids (Fig. ~~3B~~ 4A) that may interact with negatively charged phospholipids. --

Please replace paragraph 0049 on page 19 with the following amended paragraph:

-- Overall, a comparison of FAAH's structure to that of the soluble AS enzyme MAE2 reveals how a single member of a large clade of proteins has adapted to perform a specialized cellular function through the addition of discrete folding modules and without gross changes in catalytic mechanism or fold architecture (~~Fig. 4~~ Fig. 3). For example, although FAAH and MAE2 dimerize about roughly the same face, they have different relative monomer orientations. These distinct quarternary orientations produce an antiparallel and parallel alignment of the MAE2 and FAAH monomer active site entrances, respectively. The parallel orientation of FAAH monomers has important biological implications, as it should permit both subunits to function concurrently by recruiting substrates from the same membrane. Furthermore, this parallel alignment places another key structural module, the α18-α19 hydrophobic cap, on the same face of the dimer, thereby enhancing membrane binding (~~Fig. 4~~ Fig. 3). Additional sequence insertions in the FAAH protein account for other specialized features of the enzyme's structure, including its cytoplasmic channel and apolar substrate binding pocket (~~Fig. 4~~ Fig. 3). --

Please replace paragraph 0053 beginning on page 20 with the following amended paragraph:

-- ~~Figure 3~~ Figure 4 depicts the predicted membrane-binding cap of FAAH. (A) The hydrophobic helices α18 and α19 that comprise the putative membrane-binding cap are shown in green. The primary sequence of this domain (residues 404-433 of SEQ ID NO: 1) is indicated using amino acid one letter code (*29*) except for hydrophilic amino acids, which are indicated by *x*. Five of

these seven hydrophilic residues are arginine or lysine; the remaining two are serines. (B) The molecular surface of FAAH viewed from the membrane face; the observed structure demonstrates the presence of a hydrophobic cap (*top, green*), surrounded primarily by positive electrostatic potential (*bottom; blue, basic; red, acidic*). The entrance to the active site from the membrane face is indicated, as are arginine 486 and aspartate 403, which form one side of this access port. --

Please replace paragraph 0054 on page 21 with the following amended paragraph:

-- ~~Figure 4~~ Figure 3 sets forth proposed modular adaptations that convert a soluble enzyme to an integral membrane enzyme based on differences in the structures of FAAH and MAE2. The soluble enzyme, if oligomeric, reorganizes so that all active sites can concurrently access the bilayer for maximal efficiency. The addition of discrete structural elements, represented here in red, confer the new oligomerization domain (tryptophan 445 and residues 299-314; *lower left panel*) as well as a membrane binding face (*lower middle left panel*) and cytoplasmic access channel (*lower middle right panel*). The final monotopic integral membrane enzyme must also undergo mutation of key substrate binding residues in the active site to effectively recruit its hydrophobic targets from the lipid bilayer (*lower right panel*). --

Please replace the table heading for Table 5 on page 21 with the following amended heading:

-- Table 5. Residues of SEQ ID NO: 1 expected to line the interior channels of FAAH. The coordinates of the Cαs in the present structure are provided as a guide only. --

Please replace heading at line 1 on page 25 with the following amended heading:

-- ~~SEQ.ID.NO 1:~~ SEQ ID NO: 1: --